

R E M A R K S

Information Disclosure Statement Dated August 30, 2006

A copy of the Form PTO/SB/08A dated August 30, 2006 was returned with the February 24, 2008 Office Action, with the Examiner's initials next to each cited publication, except for JP 2003-500401. On said copy of the Form PTO/SB/08A dated August 30, 2006, a line was drawn through JP 2003-500401, and the following handwritten notation was made: "Not translated." On said Form PTO/SB/08A dated August 30, 2006, it was stated that an English-language abstract of JP 2003-500401 was provided and that USP 6,380,214 is a related family member of JP 2003-500401.

In view of the above, the Examiner is respectfully requested to return another copy of Sheet 1 of said Form PTO/SB/08A dated August 30, 2006, with the Examiner's initials next to all the cited publications, including JP 2003-500401.

Information Disclosure Statements Filed  
March 20, 2008 and February 1, 2008

The Examiner is respectfully requested to return fully initialed IDS Forms for the Information Disclosure Statements filed on March 20, 2008 and February 1, 2008.

Response to Restriction Requirement

1. The Examiner is respectfully requested to clarify the meaning of the word "groupie" in the following statement on page 2, lines 8 to 9 of the Office Action:

"Example 3-7 belongs in **groupie** and is deemed non-elected by applicant" [emphasis added].

2. The undersigned had a telephone interview with Examiner Solola on June 19, 2008 to clarify the scope of Group I of the November 19, 2007 Restriction Requirement, which set forth numerous example numbers. During said telephone interview, Examiner Solola said that Group I was not intended to represent a Markush listing of compounds, but rather was intended to represent a subgeneric claim of claim 1 (i.e., a claim similar to claim 1).

#### Claim Amendments

The amendments to claims 4 and 7 to 9 involve only changes in claim dependencies.

Claim 11 was amended to change the dependency and to recite a "pharmaceutically acceptable carrier" (see pages 73 and 74 of the specification) and to recite a "pharmaceutically effective amount" of the compound (see the first full paragraph on page 75 of the specification).

New method claims 14 and 15 replace original agent claims 12 and 13, respectively. New method claim 14 is further supported by pages 73 to 75 of the specification.

If new method claims 14 and 15 are withdrawn by the Examiner, rejoinder and allowance of such method claims are respectfully requested, if the compound claims which they depend on are allowed.

New claims 16 to 27 recite compounds set forth in original claim 10. Each of the compounds recited in new claims 16 to 27 were subjected to pharmacological testing, the results of which are set forth in Table 3 on page 285 of the specification.

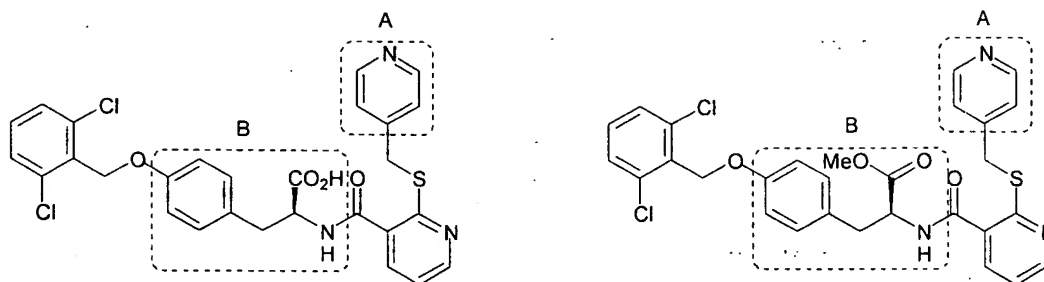
The compound of claim 16 corresponds to Example 3-1.  
The compound of claim 17 corresponds to Example 3-6.  
The compound of claim 18 corresponds to Example 3-8.  
The compound of claim 19 corresponds to Example 3-10.  
The compound of claim 20 corresponds to Example 4-1.  
The compound of claim 21 corresponds to Example 4-10.  
The compound of claim 22 corresponds to Example 4-11.  
The compound of claim 23 corresponds to Example 9-1.  
The compound of claim 24 corresponds to Example 10-1.  
The compound of claim 25 corresponds to Example 10-2.  
The compound of claim 26 corresponds to Example 12-1.  
The compound of claim 27 corresponds to Example 12-2.

The compound of claim 4-1 (i.e., the compound recited in claim 22) was the elected species set forth on page 4 of applicants' RESPONSE TO RESTRICTION REQUIREMENT filed December 14, 2007.

#### Anticipation Rejection Under 35 USC 102

Claims 1 to 11 were rejected as being anticipated by Head et al. WO 9937618 (equivalent to USP 6,329,372) for the reasons set forth beginning at the bottom of page 2 of the Office Action and continuing to the top of page 3 of the Office Action.

Head et al. disclose the following compounds:



(these compounds are hereinafter collectively referred to as "Head's Compounds").

Head's Compounds are substantially different from applicants' claimed compounds in that Head's Compounds do not have a substituted or unsubstituted amino group on the pyridine ring (portion A enclosed with a dotted line in the above compounds). Therefore, it is clear that compounds disclosed by Head et al. are not within the scope of applicants' claimed compounds.

Withdrawal of the 35 USC 102 rejection is therefore respectfully requested.

It is furthermore respectfully submitted that Head et al. do not teach or suggest applicants' present claims for the following reasons.

The structure introduced from phenylalanine (portion B enclosed with a dotted line in the above compounds) is essential for Head's Compounds, while it is not essential for the compounds

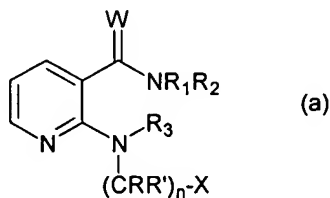
according to applicants' present claims. Moreover, the compounds disclosed in Head et al. are for use in integrin inhibitors, while applicants' claimed compounds are for use in VEGF inhibitors. That is, the compounds disclosed in Head et al. are clearly different from applicants' claimed compounds, both in chemical structure and in use. Therefore, it is respectfully submitted that one of ordinary skill in the art would not arrive at applicants' claimed compounds based on the disclosure of Head et al.

Obviousness Rejection Under 35 USC 103

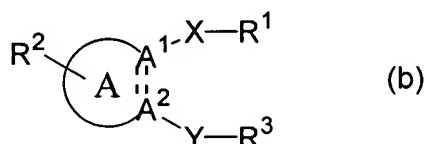
Claims 1 to 11 were rejected under 35 USC 103 as being unpatentable over Manley et al. WO 01/55114 and Chen et al. WO 02/066470, individually, in view of King, Med. Chem. Principle and Practice, (1994), pp. 206-208 for the reasons set forth on pages 3 to 5 of the Office Action.

It was admitted in the Office Action that the difference between the instant invention and that of Manley et al. and Chen et al. is that in the compounds of the prior art, applicants replaced -NH- with -S- on ring A.

It was asserted in the Office Action that Manley et al. disclose 2-amino-nicotinamide compounds represented by the following formula (a) and that such compounds possess VEGF receptor tyrosine kinase inhibitory activity:



Further, it is contended in the Office Action that Chen et al. disclose compounds represented by the following formula (b) and that such compounds possess a therapeutic effect for treating cancer, angiogenesis and other disorders:



Moreover, it was alleged in the Office Action that King discloses that the replacement of -NH- with -S- in a compound is expected to produce compounds having similar biological activity (biosterism), i.e., that -NH- and -S- are examples of bivalent equivalents.

Based on the above, the position was taken in the Office Action that it would have been obvious to try the replacement of -NH- with -S- on the ring A.

Applicants respectfully submit that their present claims patentably distinguish over the combination of Manley et al, Chen et al. and King for the following reasons.

Referring to the above compound (a) of Manley et al., it is noted that the 2-amino group is directly linked to the pyridine ring, i.e., it is an essential component for Manley et al. This means that a person having ordinary skill in the art would consider that the 2-amino group directly linked to the pyridine ring is essential for the Manley et al. compounds to have VEGF receptor tyrosine kinase inhibitory activity. Accordingly, it is respectfully submitted that there is no teaching, suggestion or

motivation in Manley et al. to replace the 2-amino group directly linked to the pyridine ring with substituents other than the amino group.

Regarding the above compound (b) of Chen et al., it is noted that the linker Y directly linked to the ring A is a group containing a nitrogen atom, such as an amino group or an imino group. This means that a person having ordinary skill in the art would consider that it is essential that the linker Y directly linked to the ring A should be a group containing a nitrogen atom, such as an amino group or an imino group. Accordingly, it is respectfully submitted that there is no teaching, suggestion or motivation in Chen et al. to replace the linker Y directly linked to the ring A with any substituent other than a group containing a nitrogen atom, such as an amino group or an imino group, i.e., other substituents not containing a nitrogen atom, e.g., substituents other than an amino group or an imino group.

King describes -S- as one example of a bivalent equivalent showing the bioisosterism of -NH-. However, there is no teaching, suggestion or motivation in King with respect of bioisosterism relating to a concrete pharmacological activity, such as VEGF receptor tyrosine kinase inhibitory activity. There is no teaching or suggestion in King for treating cancer, angiogenesis and other disorders.

Further, applicants would like to briefly discuss the concept of bioisosterism and bioisoster, introduced by H.L. Friedman in 1951. According to the definition of a bioisoster, the completely opposite properties such as inhibitors and antagonists are included in one and the same concept. This means that it is general knowledge for a person having ordinary skill in this technical field that bioisosterically equivalent drugs do

not necessarily possess the same pharmaceutical properties.

Moreover, in the case where the substituents in the above formulae (a) and (b) of Manley et al. and Chen et al., respectively, are attempted to be replaced, there exists a large number of alternatives for possible replaceable substituents. Still further, also in King, there are a large number of substituents in the same category that are considered to be bioisosters in King, and King does not specifically describe the drug efficacy of these bioisosters at all.

Consequently, there exists no rational teaching, suggestion or motivation to combine Manley et al., Chen et al. and King in view of the above comments. Further, a combination of King and Manley et al. or a combination of King and Chen et al., based on the definition of the bioisoster described above, would not lead a person having ordinary skill in the art to rationally expect a similar drug efficacy. Furthermore, in view of the above comments, since there are a large number of parameters or alternatives in Manley et al., Chen et al. and King, none of these references teach or suggest a high possibility of success. That is, it is respectfully submitted that attempts to arrive at applicants' claimed invention cannot be said to be "obvious to try."

Withdrawal of the 35 USC 103 rejection is therefore respectfully requested.

#### Double Patenting Rejection

Claims 1 to 11 were provisionally rejected under 35 USC 101 as claiming the same invention as that in claims 1 to 15 and 21 of copending application Serial No. 10/548,283.



Applicants respectfully disagree with this rejection for the following reasons.

The compounds claimed in the above-identified application are different from those in copending application Serial No. 10/548,283 in that the portion A enclosed with the dotted line as noted above (on the pyridine ring) has a  $-NR^3R^4$  group (a substituted or unsubstituted amino group) as a substituent. In the claims of copending application Serial No. 10/548,283, Y is not a substituted or unsubstituted amino group. Withdrawal of the double patenting rejection is therefore respectfully requested.

Enclosed is a Form PTO-2038 in the amount of \$1,400 for payment of 28 additional total claims.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,

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Encs.: (1) PETITION FOR EXTENSION OF TIME  
(2) Form PTO-2038

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